REMARKS

Claims 1-5, 8-11, 31, and 33-37 are pending in this application and are presented for examination.

The Office rejected claims 1-8, 11, 31, 34, 36, and 37 under 35 U.S.C. § 103(a) as being rendered obvious by U.S. Patent No. 5,780,024 ("the '024 patent"), in view of Halpern et al., *Infection and Immunity*, vol. 58, pp. 1004-09 (1990) ("Halpern"). Specifically, the Office asserted that the '024 patent discloses an *in vivo* method of delivery of a composition comprising a tetanus toxin C fragment recombinantly fused to a second protein, wherein the protein is fused downstream of the tetanus toxin C fragment. The Office also asserted that the '024 patent discloses that the fusion protein is capable of *in vivo* retrograde axonal transport and transynaptic transport into the CNS, and that it can be used for treatment of neurodegenerative diseases. *See* Office Action of April 14, 2004, at pages 3-4.

The Office acknowledged that the '024 patent fails to disclose that the C-terminal tetanus toxin C fragment should contain at least, or specifically, 11 amino acids of the B-fragment, *see id.* at 4, but it asserted that Halpern overcomes this failure by disclosing a recombinant tetanus toxin C fragment with at least 9 amino acids of the B fragment. Furthermore, the Office asserted that one of skill in the art would find it obvious to optimize the additional B fragment portion to 11 amino acids. The Office also asserted that motivation to alter the teachings of the '024 patent and of Halpern are provided by these references. *See id.* at pages 4-5.

The Office rejected Applicants' previous arguments that the '024 patent does not disclose a hybrid protein capable of transynaptic transport because "[o]ne would have

no reason to doubt the assertions of the '024 patent . . . ." *See id.* at 5. Applicants wish to clarify that their main argument regarding the '024 patent is the interpretation of that disclosure. Specifically, Applicants disagree that the '024 patent discloses a fusion protein that "undergoes *in vivo* retrograde axonal transport and transynaptic transport," an element of pending independent claims 1 and 31.

The '024 patent is purported to teach retrograde axonal transport and transynaptic transport of a fusion protein comprising the tetanus toxin C fragment, the SOD:Tet451 fusion protein, but Applicants respectfully note that no evidence of this feature is actually disclosed. The '024 patent discloses uptake and transport of the SOD:Tet451 in motor neurons in the Example provided in column 16. In this example, the SOD:Tet451 protein was injected into the tongues of mice and sections of brainstem were examined after 24 hrs. Immunoreactivity to anti-SOD-1 and anti-TTC antibodies was demonstrated in the hypoglossal motor neurons and their processes. The disclosure of the '024 patent concludes that "the SOD-1/TTC hybrid protein undergoes *retrograde transport to the cell bodies of motor neurons*, and that the observed transport is TTC-dependent." '024 patent at col. 16, lines 33-36 (emphasis added). This disclosure describes movement that is retrograde, but it is contained within the hypoglossal motor neurons and therefore is not transynaptic because it does not cross a synapse.

A very similar experiment was conducted with the claimed fusion protein of the invention, as described in Example 7 of the specification. In Example 7, a gal-TTC protein was injected into the tongue of a mouse and resulting retrograde movement through the hypoglossal structure was present after 24 hours. Like the disclosure in the

'024 patent, the instant specification concludes: "These data demonstrate that the gal-TTC hybrid protein can migrate rapidly by retrograde axonal transport as far as motoneuron cell bodies, after prior uptake by nerve terminals in the tongue." Specification at page 27.

But, in contrast to the disclosure of the '024 patent, the instant specification continues by describing the more extensive, transynaptic movement of the claimed fusion protein. Example 8 of Applicants' specification explains that "[u]p to 24 hrs post-injection, labeling was restricted to the hypoglossal nuclei. After 24 hrs, the distribution of *second order transneuronally labeled cells* in various regions of the brain was consistent and reproducible." Specification at page 29 (emphasis added). The specification continues by describing that "[i]ntense transneuronal labeling was detected in the lateral reticular formation (LPRF), where medullary reticular neurons have been reported to form numerous projections onto the hypoglossal nucleus . . . ." *Id.* Furthermore, "[t]ransynaptic transport of the gal-TTC protein was also detected in the pontine reticular nucleus caudal (PnC), the locus coeruleus (LC), the medial vestibular nucleus (MVe) and in a few cells of the inferior vestibular nucleus (IV)." *Id.* at 30. Finally, the specification discloses that the fusion protein of the invention even moves across other synapses to arrive at "putative third order cell groups related to the hypoglassal nucleus . . . ." *Id.* These features are not described in the '024 patent.

The significance of moving through neurons of second or higher order is explained in the specification, as follows: "The different stages of the neuronal transport are through [1] the neuromuscular junction, [2] the motoneuron, also called the first order neuron, [3] the synapse at any stage between the neurons of different order,

neuron of order second to fourth order . . . ." Specification at 12-13. Therefore, transport through the hypoglossal motor neuron and then to second order neurons in various regions of the brain encompasses movement through step [3] described above, across a synapse or *transynatic* movement.

Such transynaptic movement of step [3] is clear from the results with the claimed fusion protein in Example 8 of the instant specification, where the fusion protein is shown to move from hypoglossal motor neurons across synapses to other neurons, such as the pontine reticular nucleus caudal, the locus coeruleus, the medial vestibular nucleus, and the cells of the inferior ventricular nucleus. *See* specification at 30. In contrast, transynaptic movement is not demonstrated at all in the '024 patent. Instead, the '024 patent only describes transport through the hypoglossal motor neuron, which would be characterized as stage [2] above.

Because the '024 patent does not disclose transynaptic transport, the Office must provide a prior art reference that discloses this element in order to make a *prima facie* case of obviousness. *See In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The Office combined the Halpern reference with the '024 patent in making its rejection under 35 U.S.C. § 103, but Halpern does not disclose a fusion protein that cures the deficiencies of the '024 patent. While Halpern may disclose the use of tetanus toxin C fragment with at least nine amino acids of the B fragment, it does not demonstrate transynaptic transport.

The Office asserted that Applicants' arguments regarding the lack of a demonstration of transynaptic transport in the prior art was unpersuasive because of the

reference to Kuypers and Uglioni, *Trends Nuerosci.*, vol. 13, pp. 71-75 (1990) ('Kuypers"), in the specification. *See* Office Action of April 14, 2004, at 5. Applicants respectfully note that Kuypers discloses neural transport of proteins using viral vectors, not tetanus toxin hybrid proteins. Therefore, Applicants' argument that others have failed to show transynaptic transport – with a hybrid protein such as that of the claimed invention – is correct.

In addition, Applicants respectfully disagree with the Office's assertion that there would have been a motivation to combine the '024 patent and Halpern. Although the Office asserted that Halpern would have provided the motivation to one skilled in the art to make the claimed fusion protein, the claim limitation of "at least 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C" is not taught by Halpern. Nor does Halpern provide any reason to choose at least 11 amino acids of fragment B. Evidence that Halpern would not have provided any motivation to one skilled in the art to chose this limitation can be found in one of Halpern's later publications. The cited Halpern reference was published in 1990, but in 1993, Halpern et al. wrote: "It is not known if binding to ganglioside is sufficient to trigger the retrograde axonal transport of Hc [the heavy chain of tetanus toxin], or if internalization into vesicles and transport is a more complex process." Halpern et al., *J. Biol. Chem.*, vol. 268, pp. 11188-92 (1993) at 11192. This indicates that even three years after the Halpern reference cited by the Office cited as providing motivation to choose "at least 11 amino acid resides of fragment B," Halpern did not understand what factors affect retrograde transport. Thus, Halpern could not have provided motivation to

combine its teaching with the '024 patent so that one of skill in the art would find the claimed invention to be obvious.

On pages 6 and 7 of the Office Action of April 14, 2004, the Office rejected claims 9 and 10 as being obvious in view of the '024 patent, Halpern, and Fishman et al., *J. Neurosci.*, vol. 98, pp. 311-325 (1990) ("Fishman"). Claims 9 and 10 are dependent on claim 1, which requires that the fusion protein comprise fragment C and at least the 11 amino acids of fragment B that immediately precede the amino terminus of fragment C and that the fusion protein undergo transynaptic transport. One of skill in the art would not expect that Fishman could cure the deficiencies of either the '024 patent or Halpern because the statement in the Discussion section of Fishman highlighted by the Office, *see* Fishman at 323 ("Linkage with CF [fragment C] also may enhance the stability of chosen protein within the CNS as well as promote its spread by transsynaptic transport."), is mere speculation, highlighted by the term "may." Not only would the speculative nature of this statement dissuade one of skill in the art from relying on Fishman to make the claimed invention, it creates doubt about any data regarding transynaptic transport that Fishman may have disclosed because the authors do not seem convinced. This is in direct contrast to Applicants' statement about an advantage of the claimed invention providing "better transport of the fragment inside the organism compared with fragment C." Specification at 6. Accordingly, Applicants respectfully request that the rejection of claims 9 and 10, in light of the '024 patent, Halpern, and Fishman be withdrawn.

On pages 7-8 of the Office Action of April 14, 2004, the Office rejected claims 1-8, 11, 31, and 33-36 in light of the '024 patent, Halpern, and U.S. Patent No. 6,159,948

("the '948 patent"), under 35 U.S.C. § 103. The Office asserted that the '948 patent discloses treatment of neurodegenerative disorders by administration of the SMN protein. As explained above, though, the '024 patent and Halpern fail to disclose a tetanus toxin fusion protein that is capable of transynaptic transport and so do not render the claimed invention obvious. The '948 patent does not remedy this deficiency, and, therefore, its combination with the '024 patent and Halpern does not render the claimed invention obvious either. Accordingly, Applicants request that this rejection be withdrawn.

On pages 8-10, the Office rejected claims 1-8, 11, 31, 34, and 36 as being rendered obvious by Francis, et al., *J. Biol. Chem.*, vol. 270, pp. 15434-15442 (1995) ("Francis") and Halpern. The Office asserted that Francis teaches transynaptic transport of a tetanus toxin hybrid protein because it states "the hybrid protein could access other central nervous system neurons . . . given the ability of TTC to undergo retrograde transynaptic transport." *See* Office Action of April 14, 2004, at 10, quoting Francis at 15441, col. 1. Unlike the instant specification, Francis does not provide any data showing transynaptic transport, for example, with staining of central nervous system tissue sections. Instead, Francis provides only *in vitro* data of internalization of a fusion fragment C protein using cultured neural cells. *See* Francis at 15437, col. 2, through 15440, col. 1); *see also*, specification at 3, (discussing the results of Francis). Therefore, Francis's statement regarding transynaptic transport is mere speculation. Without a disclosure of a hybrid protein that can achieve transynaptic transport, the references cited by the Office do not render the claimed invention obvious, and Applicants respectfully request that the rejection be withdrawn.

Finally, on pages 10-11 of the Office Action of April 14, 2004, the Office rejected claims 6-8, 11, 31, 33, 35, and 36 under 35 U.S.C. § 103, in light of Francis, Halpern, and the '948 patent. Applicants note that claims 6 and 7 have been cancelled. Each of claims 8, 11, 33, 35, and 36 ultimately depends on claims 1 or 31, which requires that the fusion protein undergo transynaptic transport. As explained above, neither Francis, Halpern, nor the '948 patent discloses a fusion protein that is capable of transynaptic transfer. Therefore, the combination of these references does not anticipate the inventions claimed in claims 1 or 31, or any of the claims depending on them. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 10, 2004

By: _____

Deborah Katz
Reg. No. 51,863
Phone: 202-408-4382
Fax: 202-408-4400
E-mail: deborah.katz@finnegan.com